The *DAO* gene is associated with schizophrenia and interacts with other genes in the Taiwan Han Chinese population

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Abstract

Background: Schizophrenia is a highly heritable disease with a polygenic mode of inheritance. Many studies have contributed to our understanding of the genetic underpinnings of schizophrenia, but little is known about how interactions among genes affect the risk of schizophrenia. This study aimed to assess the associations and interactions among genes that confer vulnerability to schizophrenia and to examine the moderating effect of neuropsychological impairment.

Methods: We analyzed 99 SNPs from 10 candidate genes in 1,512 subject samples. The permutation-based single-locus, multi-locus association tests, and a gene-based multifactorial dimension reduction procedure were used to examine genetic associations and interactions to schizophrenia.

Results: We found that no single SNP was significantly associated with schizophrenia. However, a risk haplotype, namely *A-T-C* of the SNP triplet rsDAO7-rsDAO8-rsDAO13 of the *DAO* gene, was strongly associated with schizophrenia. Interaction analyses identified multiple between-gene and within-gene interactions. Between-gene interactions including *DAO*DISC1*, *DAO*NRG1* and *DAO*RASD2* and a within-gene interaction for *CACNG2* were found among schizophrenia subjects with severe sustained attention deficits, suggesting a modifying effect of impaired neuropsychological functioning. Other interactions such as the within-gene interaction of *DAO* and the between-gene interaction of *DAO* and *PTK2B* were consistently identified regardless of stratification by neuropsychological dysfunction. Importantly, except for the within-gene interaction of *CACNG2*, all of the identified risk haplotypes and interactions involved SNPs from *DAO*.

Conclusions: These results suggest that *DAO*, which is involved in the N-methyl-D-aspartate receptor regulation, signaling and glutamate metabolism, is the master gene of the genetic associations and interactions underlying schizophrenia. Besides, the interaction between *DAO* and *RASD2* has provided an insight in integrating

the glutamate and dopamine hypotheses of schizophrenia.

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